Update on systemic therapies for atopic dermatitis

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Purpose of review
Although many atopic dermatitis patients can be treated satisfactorily with topical medications and systemic anti-itch approaches, a smaller subset require more aggressive systemic therapies. Familiarity with the latest literature on the benefits and risks of these treatments will enable the clinician and patient to select the most appropriate therapy based on the patient's lifestyle, assessments of risks and comorbidities.

Recent findings
Additional data have come to light altering the risk and benefit ratio of certain systemic atopic dermatitis therapies. In 2011, we saw several head-to-head, randomized controlled trials of established systemic medications for the treatment of atopic dermatitis. A few new systemic atopic dermatitis treatments have highlighted how targeted therapies may inform us about disease pathogenesis.

Summary
In light of the risk of hepatosplenic T-cell lymphomas, a greater degree of caution is warranted in the use of azathioprine. NBUVB, mycophenolate, and methotrexate remain the reasonable first-line systemic treatment options for atopic dermatitis. A brief run-in with high-dose cyclosporine to clear atopic dermatitis followed by maintenance with low-dose cyclosporine or cellcept – both of which have better risk and benefit ratios is a reasonable approach. Interferon gamma and intravenous immunoglobulin, although expensive, are potential options, and possibly most ideal for atopic dermatitis patients plagued by significant viral skin infections such as eczema herpeticum. A better understanding of the immunopathogenesis of atopic dermatitis will come with the exploration of novel targeted therapies.

Keywords
atopic dermatitis, immunomodulation, phototherapy, systemic therapies

INTRODUCTION

Atopic dermatitis is a chronic inflammatory skin disorder characterized by intensely pruritic eczematous skin lesions that typically develop in age-specific anatomical locations. There are numerous theories proposed to explain the development of this common disorder. For years, the major theory was that patients had an aberrant and robust Th2 adaptive immune response to largely innocuous environmental antigens. Recent research highlights the importance of skin barrier abnormalities and an inadequate host response to common cutaneous microbes as other highly plausible mechanisms that might predispose individuals to develop atopic dermatitis. Allergen and irritant identification and avoidance, moisturizing the skin, as well as topical prescription anti-inflammatory therapies have been the mainstay of treatment for mild-to-moderate atopic dermatitis. Although some mild cases of atopic dermatitis can be managed with bland emollients alone, most patients require treatment with either topical corticosteroids or calcineurin inhibitors. When patients fail these interventions and measures to minimize environmental influences, systemic options are often considered. In this review, we will comment on the studies published primarily in 2011 that may help direct a clinician's choice of systemic therapies for atopic dermatitis.

CYCLOSPORINE, MYCOPHENOLATE MOFETIL, AND MYCOPHENOLIC ACID

Cyclosporine (CSA) and mycophenolate mofetil, the prodrug of mycophenolic acid, are immunosuppressants approved to prevent transplant rejection [1,2]. In light of the potential for nephrotoxicity and hypertension with chronic CSA therapy, it is

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KEY POINTS

- Mycophenolate sodium can be used to maintain the improvement in atopic dermatitis achieved from a brief course of high-dose cyclosporine.
- Methotrexate and azathioprine have similar efficacy and adverse effect profiles at doses used to treat moderate-to-severe atopic dermatitis in adults.
- In a small case series ($n = 3$), tocilizumab, a monoclonal antibody against the IL-6 receptor, was effective in clearing atopic dermatitis but appears to carry an increased risk of bacterial infections.
- PPAR-gamma and alpha agonists may have a role in either prevention or treatment of atopic dermatitis because of their anti-inflammatory and barrier restoration properties.
- In 2011, the FDA added a black box warning to azathioprine, 6-mercaptopurine, infliximab and adalimumab indicating the increased risk of developing hepatosplenic T-cell lymphoma, a highly aggressive malignancy. This risk appears to be greatest when these drugs are combined with other immunosuppressants. To date, this lymphoma has not been reported in atopic dermatitis patients.

challenging to determine when and in which atopic dermatitis patients this medication should be considered. Fifty-five adult atopic dermatitis patients who were unresponsive to topical therapies were treated for 6 weeks with high-dose CSA (5 mg/kg/day divided into two doses) as an acute management strategy [3▪▪]. This was followed by randomization to receive maintenance treatment with either CSA 3 mg/kg/day or enteric-coated mycophenolate sodium (1440 mg/day) for 30 weeks followed by a 12-week follow-up period. During the run-in phase, all patients experienced a significant improvement in SCORAD (SCORing Atopic Dermatitis) and serum thymus and activation-regulated chemokine (TARC) levels. Although initially patients randomized to CSA maintenance had better control of their atopic dermatitis, by 10 weeks the average SCORAD values were comparable. In the follow-up phase, the mycophenolate-treated arm maintained greater disease control than those who had received CSA as a maintenance treatment. Although the potential for nephrotoxicity and hypertension relegates CSA to a third-line choice as an atopic dermatitis maintenance strategy, this study demonstrated the value of using high-dose CSA to achieve rapid initial control of atopic dermatitis prior to switching to an arguably safer longer-term medication (i.e. mycophenolate). This is an interesting study that suggests a treatment approach whereby high-dose CSA is used to achieve rapid, short-term control of atopic dermatitis and maintenance of this benefit is achieved with safer immunosuppressants. This approach avoids the adverse effects, which commonly arise with chronic CSA use.

TOCILIZUMAB

Tocilizumab is an IL-6 receptor antagonist, FDA-approved in 2008 for the treatment of rheumatoid arthritis [4]. Recent publications have reported on the off-label use of tocilizumab to treat other systemic inflammatory disorders including systemic sclerosis, systemic lupus erythematosus, large vessel vasculitides and polymyositis [4]. Navarini *et al.* [5▪] reported their experience treating three adult atopic dermatitis patients whose disease was refractory to topical corticosteroids, topical calcineurin inhibitors and phototherapy. Two of these patients had also failed CSA. These patients were treated with IV infusions of 8 mg/kg tocilizumab every 4 weeks. Within 6 weeks of initiating tocilizumab therapy, all three patients reported resolution of pruritus and within 3 months, their Eczema Area and Severity Index (EASI) scores dropped by more than 50%. In addition, all patients were able to taper their topical therapies [5▪]. The only significant side-effects were bacterial infections observed in two of the three patients. One patient experienced left heel bursitis secondary to streptococcus 10 months into therapy. The other patient developed an uncomplicated bacterial conjunctivitis 5 months after initiating tocilizumab. These infections resolved with discontinuation of tocilizumab and appropriate therapies. In a large trial of rheumatoid arthritis patients treated with identical dosing of tocilizumab (8 mg/kg), the rate of serious infections tripled (from 1 to 3%) [6], suggesting that IL-6 blockade may enhance infection risks. Further studies are warranted to better characterize the efficacy and safety of tocilizumab in atopic dermatitis patients.

AZATHIOPRINE

Like many immunosuppressants, azathioprine, which is a purine analog, was initially developed in the 1960s to prevent organ rejection. It has also been used to treat a number of immunologic diseases including pemphigus vulgaris [7], rheumatoid arthritis [8], inflammatory bowel disease [9], as well as atopic dermatitis [10].

An increased risk of malignancy (including non-Hodgkin's lymphomas [11] and sarcomas [12,13]) is a recognized risk of long-term azathioprine treatment in patients receiving treatment to prevent transplant rejection or to manage inflammatory

bowel disease [14]. This past year azathioprine received a black box warning about the potential for a rare but frequently lethal lymphoma called hepatosplenic T-cell lymphoma (HSTCL) [15]. HSTCL responds poorly to chemotherapy and bone marrow transplantation [16▪▪]. Initially, it was thought to occur primarily in young men with Crohn's disease who were also treated with tumor necrosis factor (TNF) antagonists, but a recent review of 25 HSTCL cases indicates the profile of susceptible patients is a bit broader [16▪▪]. Over a third of the cases described do not fit this high-risk patient profile. Three of the cases were in patients with rheumatoid arthritis, which indicates that the underlying disease process may play less of a role than the azathioprine. Additionally, 3 of the 25 patients with HSTCL were treated with methotrexate in conjunction with a TNF antagonist (and not azathioprine). Importantly, none of the reported HSTCL cases was in atopic dermatitis patients receiving these drugs. Further studies are warranted to determine whether long-term treatment with azathioprine poses a risk for the development of HSTCL in atopic dermatitis patients.

METHOTREXATE

Methotrexate was originally developed as a safer chemotherapeutic alternative to the folate analog, aminopterin, for the treatment of childhood acute lymphoblastic leukemia. Methotrexate is an antimetabolite that directly competes with dihydrofolic acid for the binding site of dihydrofolate reductase. The resulting decrease in tetrahydrofolate inhibits cellular proliferation by limiting the synthesis of DNA, RNA, and several amino acids. In autoimmune diseases, it appears that methotrexate may also act by suppressing intercellular adhesion molecule-1 (ICAM-1) and cutaneous lymphocyte-associated antigen on T-cells [17]. It has been used to treat malignancy, autoimmune diseases and inflammatory disorders like psoriasis and atopic dermatitis.

Prior to 2011, there had been no randomized controlled trials (RCTs) to demonstrate the efficacy of methotrexate in the treatment of atopic dermatitis. Schram *et al.* [18▪] conducted a study of 42 adult atopic dermatitis patients randomized to either methotrexate 10 mg weekly or azathioprine 1.5 mg/kg/day for 12 weeks. Patient dosing was titrated upward until they either achieved 25% reduction in disease activity or reached the maximum dose allowed in the study (22.5 mg/week methotrexate, 2.5 mg/kg/day azathioprine). Following this, patients entered a 12-week follow-up period in which patients and providers were allowed to either continue with their current medication or alter the treatment plan as per normal clinical practice. The two medications performed similarly in a number of disease severity measures including SCORAD, IgE (immunoglobulin E), EASI, and serum TARC both during the initial 12 weeks of treatment and in the 12-week follow-up phase [18▪]. A significant improvement in SCORAD was observed in both methotrexate (42%) and azathioprine (39%) treated patients at 12 weeks. Methotrexate had a similar side-effect profile to azathioprine with the exception of lymphopenia, which was only observed in azathioprine-treated patients ($P = 0.02$) [18▪]. These same patients experienced a trend toward more infections ($P = 0.19$). This study suggests that methotrexate and azathioprine have similar efficacy at the doses tested, but methotrexate may have a slightly more favorable side-effect profile. It would have been nice to see the relative efficacy of these treatments when methotrexate was increased to 25 mg/ week – a dose used not uncommonly to achieve clearance in patients with psoriasis.

INTERFERON GAMMA

Interferon gamma (IFNγ) is an important part of the host immune response, particularly against viruses. It is FDA-approved as a subcutaneous injection to reduce the frequency and severity of infections in chronic granulomatous diseases [19] and to treat malignant osteopetrosis [20]. In a recently published case series of pediatric atopic dermatitis patients with eczema herpeticum, it was suggested that IFNγ and intravenous immunoglobulin (IVIG) are less likely to enhance the cutaneous viral susceptibility of these patients than other immunomodulators [21▪]. In summary, although IFNγ is more expensive than CSA or methotrexate, it may be useful as a treatment for moderate-to-severe atopic dermatitis patients who have a history of recurrent skin infections with herpes simplex, molluscum contagiosum or human papilloma viruses. This is a particularly tough population to treat and more studies are needed to determine how and if their treatment should differ from atopic dermatitis patients who do not have problems with cutaneous viral infections.

INTRAVENOUS IMMUNOGLOBULIN

IVIG is FDA approved for the treatment of pediatric HIV infections, chronic lymphocytic leukemia, idiopathic thrombocytopenic purpura, Kawasaki's disease, primary immunodeficiencies, chronic inflammatory demyelinating polyneuropathy, and kidney transplantation when there is a high likelihood of rejection (ABO incompatibility or a

recipient with markedly elevated antibody titer). There are a number of theories proposed for IVIGs mechanism of action in these diseases. These include competing for Fc receptors of macrophages and other antigen presenting cells, altering production of various cytokines, neutralization of pathogens that exacerbate or initiate the disease process, neutralization of autoantibodies, increasing the turnover rate of antibodies, decreasing B and T cell proliferation, increasing the binding affinity of glucocorticoid receptors, inhibiting complement-mediated damage, inhibition of Fas-mediated cell death, and binding of cellular adhesion molecules [22]. Treatment of severe refractory atopic dermatitis with IVIG has yielded conflicting results and therefore it is not widely used. Nevertheless, IVIG has been shown to contain high concentrations of staphylococcal toxin-specific neutralizing antibodies that can inhibit the in-vitro activation of T cells by staphylococcal toxins [23]. In 2011, a small case series of four highly allergic atopic dermatitis patients (three pediatric/one adult) demonstrated significant improvement with monthly infusions of IVIG (0.5–1.0 g/kg/dose), based on SCORAD assessments, but this benefit was only observed in pediatric cases [24]. This is consistent with the prior literature that suggests this treatment is most effective in pediatric cases as either a stand-alone treatment or more commonly as add-on therapy.

In a RCT of IVIG (2.0 g/kg/month for 3 months) to treat moderate-to-severe pediatric atopic dermatitis patients ($n = 40$), a statistically significant reduction in SCORAD was observed after three infusions which was even more impressive by 3 months after discontinuing treatment [25]. Unfortunately, disease relapse was observed by 6 months after discontinuing treatment. These improvements were accompanied by reductions in serum IL-5/IFNγ ratio, soluble ICAM-1, and eosinophil cationic protein levels, but no changes were noted in total eosinophil counts or serum total IgE values. Additional RCT are needed to determine the optimum dose of IVIG for clearance and maintenance and the patient population most likely to respond to this therapy. As IVIG is an expensive treatment, with an unclear mechanism of action, it should generally be relegated to a last resort treatment approach and probably only in pediatric atopic dermatitis patients.

PPAR-γ ANTAGONISTS (THIAZOLIDINEDIONES)

Thiazolidinediones were originally approved for the treatment of type 2 diabetes mellitus. These drugs activate the nuclear receptor, peroxisome proliferator-activated receptor gamma (PPAR-γ), which is expressed on adipocytes and most immune cells. Activation of PPAR-γ enhances the response to insulin and decreases the production of a number of proinflammatory cytokines including IL-6 and TNF-α [26]. PPAR-γ agonists have been explored as treatments for a number of inflammatory diseases including psoriasis, asthma, and focal segmental glomerulosclerosis.

The potential benefit of this class of drugs was first noted in a retrospective case series of six patients with recalcitrant atopic dermatitis who improved with the addition of rosiglitazone [27]. A recent publication utilized a mouse model of atopic dermatitis, referred to as the Nc/NgaTnd mice, to evaluate whether systemic administration of rosiglitazone was effective [28▪]. Rosiglitazone suppressed the activation of dendritic cells and delayed the development of atopic dermatitis but had no effect on established atopic dermatitis. This observation suggests that PPAR-γ agonists may also inhibit dendritic cell functions by suppressing the expression of costimulatory molecules and the release of inflammatory mediators. Both PPAR-γ and PPAR-α agonists have been shown to normalize epidermal differentiation [29], suggesting that they also have potential as barrier repair treatments. The topical application of a PPAR-α agonist decreased the clinical severity of a murine allergic contact sensitization model, which was associated with improvement in skin barrier function and reduced tissue inflammation [30]. In summary, PPAR-γ and PPAR-α agonists, which have both anti-inflammatory and barrier restorative activity, may be reasonable treatment options for established atopic dermatitis or may have their greatest effect as preventive strategies.

PHOTOTHERAPY

Phototherapy has long been used to treat a wide variety of dermatologic conditions as well as seasonal affective disorder and circadian rhythm disorders. The superiority of narrow-band UVB (NBUVB – 311–313 nm) [31] and high-dose UVA_1 (340–400 nm) [32,33] in treating atopic dermatitis over previously used approaches (broadband UVB and PUVA) is now quite clear. Unfortunately, even NBUVB, the most effective phototherapy approach, achieves only about 50% complete clearance rates in atopic dermatitis patients, whereas the majority of psoriasis patients get almost complete clearance [34].

A large ($n = 180$ patients), multicenter RCT demonstrated that 10% Dead Sea salt baths with simultaneous NBUVB therapy was superior to NBUVB

alone in treating atopic dermatitis [35]. The authors observed a 26% difference in the two treatment groups as assessed by SCORAD measurements after 6 months of therapy. A RCT crossover trial to test the relative effectiveness of NBUVB, bath-PUVA, and 3% Dead Sea salt bath plus NBUVB is currently enrolling (NCT01402414) and may help sort out the best phototherapy approach for atopic dermatitis patients.

A recent, open-label, prospective study [36] of 12 moderate-to-severe atopic dermatitis patients treated with three times per week NBUVB treatments identified several biomarkers that correlated with disease improvement as measured by SCORAD. All patients had at least a 50% improvement in their disease after 12 weeks of treatment. This improvement was accompanied by decreased expression of T_H2 and T22 cytokines, normalization of epidermal barrier and hyperplasia genes, and reduction in the dermal infiltrate. This study suggests that reducing the inflammation characteristic of atopic dermatitis skin lesions will also reverse at least some of the epidermal defects – a validation of the inside-out theory of atopic dermatitis (e.g. immune-generated epidermal dysfunction). Importantly, this study sets a new bar that all interventional studies should aspire to, namely, comparing objective measures of treatment efficacy with biomarkers of pathways relevant for disease pathogenesis.

Lastly, heliotherapy, or high-dose natural sunlight exposure typically obtained in specific locations (e.g. the Canary Islands and the Dead Sea), has been shown to be effective in treating atopic dermatitis [37,38]. Several groups are beginning to evaluate whether these benefits can be obtained in an office setting using full-spectrum light therapy (FSL – 320 nm–5000 nm) [39].

In summary, phototherapy is a useful adjunct treatment in atopic dermatitis patients but is unfortunately not as effective in atopic dermatitis as it is in psoriasis. We have little information about the long-term side effects of NBUVB, especially in our pediatric patients who might undergo treatment for many years. Until this increased risk is assessed, we think it is best to use phototherapy as an intermittent treatment approach especially in the pediatric atopic dermatitis population.

CONCLUSION

The clinicaltrials.gov website currently lists 55 actively enrolling interventional studies for atopic dermatitis (http://clinicaltrials.gov, accessed 30 March 2012). Our greater understanding of the immunopathogenesis of atopic dermatitis is beginning to drive much needed clinical trials in this common but inadequately managed disorder. Our current approach to the treatment of atopic dermatitis has focused on identifying and minimizing allergen exposure and reducing the Th2 predominant tissue inflammation. With the recognition that this is a disease mediated at least in part by epidermal barrier disruption as well as the release of potent tissue-derived adjuvants and cutaneous innate immune defects, we are likely to see therapies developed that begin to address these other defects. We hope this multipronged approach will provide greater relief for our patients than our current treatments have been able to achieve. It is certainly possible that an anti-Th2/T22 treatment strategy may also help repair some of the barrier defects, as the expression of a number of key epidermal proteins are inhibited by the cytokines released by these T cells (e.g. IL-4, IL-13, and IL-22). In summary, we have reviewed key publications from 2011 that have reported on the safety and efficacy of both new and previously used systemic treatments for patients with moderate-to-severe atopic dermatitis.

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Conflicts of interest

There are no conflicts of interest.

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